

PATENT COOPERATION TREATY

From the

INTERNATIONAL PRELIMINARY-EXAMINING-AUTHORITY SOUTHAMPTON

To:

HARDING, Charles T
D YOUNG & CO
21 New Fetter Lane
London EC4A 1DA
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year)

16.01.2001

Applicant's or agent's file reference
P005743WO CTH

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/04295

International filing date (day/month/year)
17/12/1999

Priority date (day/month/year)
18/12/1998

Applicant

UNIVERSITY OF BATH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hundt, D

Tel. +49 89 2399-8042




PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P005743WO CTH	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/04295	International filing date (<i>day/month/year</i>) 17/12/1999	Priority date (<i>day/month/year</i>) 18/12/1998
International Patent Classification (IPC) or national classification and IPC A61K31/706		
Applicant UNIVERSITY OF BATH et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 12/07/2000	Date of completion of this report 16.01.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seegert, K Telephone No. +49 89 2399 8409	



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04295

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-35 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04295

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 10 with respect to IA.

because:

- ☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 3-5

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04295

	No:	Claims	1,2,6-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-9,11-18
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04295

Section III

1. Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. Reference is made to the following documents:

- D1: WO 98 43992 A (UNIV BATH ;GALIONE ANTONY (GB); ISIS INNOVATION (GB); POTTER BARRY) 8 October 1998 (1998-10-08) cited in the application
- D2: GUSE A.H.: 'Ca²⁺ Signaling in T-Lymphocytes' CRITICAL REVIEWS IN IMMUNOLOGY, vol. 18, no. 5, 1998, pages 419-448, XP000872445
- D3: GUSE A.H. ET AL: 'Ca²⁺ Entry Induced by Cyclic ADP-ribose in Intact T-Lymphocytes' THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 13, 1997, pages 8546-8550, XP000872862

If not indicated otherwise, the relevant passages are those indicated in the International Search Report.

2. The subject-matter of the present application relates to the use of compounds capable of antagonising a sustained cADPR-mediated rise in intracellular Ca levels in a T-cell in the manufacture of a medicament for modulating T cell activity. The preferred compounds are cADPR analogues according to general formula (2). The preferred therapeutic application is the treatment of autoimmune diseases (claims 1 - 10). The application is further directed to screening methods (claims 11 - 13), to first medical uses (claim 14), to compounds (claim 15) and to processes (claims 16 - 18).
3. Document D1 discloses compounds of formula (2) and their cADP-ribose antagonising effects, e.g. in T-cells (see page 12, line 28 - page 13, line 1,

claims). According to figure 1 and page 22 of the description the activation of ADP-ribosyl cyclase activity is also tested. No therapeutic use is disclosed. Therefore the teaching of D1 is considered novelty destroying to the subject-matter of claims 11 - 13, 15 - 18.

4. Document D2 is a review article dealing with the Ca signalling effects in lymphocytes. In particular, D2 discloses that compounds of general formula (2) antagonise the cADPR induced calcium releasing effects in T-cells. D2 further teaches that the known immunosuppressant FK506 may act via this mechanism as well (see in particular page 425, right-hand column, penultimate paragraph). Finally in the conclusion on page 440 D2 suggests that the discovery of cADPR and its mechanism of activation of a channels in T-cells may have implication for the development of immune suppressive drugs.

The teaching of D2 is therefore considered novelty destroying to claims 1, 2, 6-10, 13-18 of the present application.

Summarizing the above, the subject-matter of claims 1, 2, 6-18 does not meet the novelty requirements of Article 33 (2) PCT.

5. As for claims 3 - 5, the novelty requirements of Article 33 (2) PCT are fulfilled, since the prior art does not disclose the specific compounds of formula (2) for therapeutic modulation of T cell activity. However, knowing from D2 that interference with cADPR would be therapeutically useful in immunosuppressant therapy and knowing further from e.g. D1 and D3 that these compounds have cADPR antagonistic effects, it would have been obvious to the skilled person to use these compounds for the indicated purpose. Therefore the requirements for inventive step as laid down in Article 33 (3) PCT are not met.
6. For the assessment of present claim 1 - 10, 14 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04295

a compound for the manufacture of a medicament for a new medical treatment.

Section VI

The following document may be considered relevant tin certain Contracting States:

EP-A-0 953 572 (priority: 28/04/98, filing: 28/04/99, publication: 03/11/99)

Section VIII

1. The functional definition of the compounds used in claims 1 and 2 is not sufficiently clear in order to enable the skilled person to perform the invention. It appears further that it would be an undue burden to the skilled person to find out which compounds are encompassed by the scope of the claims.
2. Similarly, the subject-matter of claim 15 lacks clarity since it is not defined by any technical features.
3. Claims 16 - 18 appear to relate to processes of manufacturing the compounds or compositions used in the present application, however without defining sufficient features for making them. Therefore these claims do not meet the requirements of Article 6 PCT.

PATENT COOPERATION TREATY

SOUTHAMPTON
10-5-00
MAR 2000

From the INTERNATIONAL SEARCHING AUTHORITY

PCT *DS CTM*
Receipt noted

To:
D. YOUNG & CO.
Attn. HARDING, Charles
21 New Fetter Lane
London EC4A 1DA
UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 10/03/2000	
Applicant's or agent's file reference P005742WO CTH	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB 99/ 04295	International filing date (day/month/year) 17/12/1999
Applicant UNIVERSITY OF BATH et al.	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <div style="text-align: center;"> Véronique Bailou </div>
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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

NOTES FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P005742W0 CTH	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 04295	International filing date (day/month/year) 17/12/1999	(Earliest) Priority Date (day/month/year) 18/12/1998
Applicant UNIVERSITY OF BATH et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

CYCLIC ADENOSINE DIPHOSPHATE RIBOSE ANALOGUES FOR MODULATING T CELL ACTIVITY

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04295

Box I Observations where certain claims were found uns archabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,6-10,14-18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,6-10,14-18

Present claims 1,2,6-10,14-18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds or uses claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those compounds disclosed in the examples and functionally related compounds, in particular those relating to the compounds of general formula (2).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Compounds capable of antagonising a sustained cADPR-mediated rise in intracellular Ca^{2+} levels in a T cell, said rise being in response to stimulation of the T cell receptor/CD3 complex of the T cell, methods for identifying the same and their use in modulating T cell activity are described. The preferred compounds are cyclic adenosine diphosphate ribose analogues.

INTERNATIONAL SEARCH REPORT

International Application No

PC 99/04295

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/706 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 43992 A (UNIV BATH ; GALIONE ANTONY (GB); ISIS INNOVATION (GB); POTTER BARRY) 8 October 1998 (1998-10-08) cited in the application page 12, line 28 -page 13, line 1; claims	11-13, 15-18
Y	---	1-18
P,X	EP 0 953 572 A (BIOMOLECULAR ENGINEERING RESEA) 3 November 1999 (1999-11-03) claims --- -/-	1-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

15 February 2000

Date of mailing of the international search report

10.03.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Seegert, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT 99/04295

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GUSE A.H.: "Ca ²⁺ Signaling in T-Lymphocytes" CRITICAL REVIEWS IN IMMUNOLOGY, vol. 18, no. 5, 1998, pages 419-448, XP000872445 page 425	1,2,6-18
Y	"Conclusion" page 440	1-18
X	--- GUSE A.H. ET AL: "Ca ²⁺ Entry Induced by Cyclic ADP-ribose in Intact T-Lymphocytes" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 13, 1997, pages 8546-8550, XP000872862 abstract	11-13, 15-18
Y	---	1-18
P,X	--- GUSE A.H. ET AL: "Regulation of Calcium Signalling in T Lymphocytes by the Second Messenger Cyclic ADP-ribose" NATURE, vol. 398, no. 6722, 4 March 1999 (1999-03-04), pages 70-73, XP000872858 the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PO 8 99/04295

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9843992	A	08-10-1998	AU 6843998 A	22-10-1998
EP 0953572	A	03-11-1999	JP 11310596 A	09-11-1999

PATENT COOPERATION TREATY

SOUTHAMPTON

13 SEP 2000

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To: HARDING, Charles T D YOUNG & CO 21 New Fetter Lane London EC4A 1DA GRANDE BRETAGNE	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">MONEY 12</td> <td style="width: 20px;"></td> <td style="width: 20px;"></td> </tr> <tr> <td style="padding: 2px;">ORDER</td> <td></td> <td></td> </tr> <tr> <td style="padding: 2px;">DATE</td> <td style="padding: 2px;">22-12-00</td> <td></td> </tr> <tr> <td style="padding: 2px;">TIME</td> <td style="padding: 2px;">05 SEP 2000</td> <td></td> </tr> <tr> <td colspan="3" style="padding: 2px; text-align: center;"> DSC TH <i>Reardo noted</i> </td> </tr> </table>	MONEY 12			ORDER			DATE	22-12-00		TIME	05 SEP 2000		DSC TH <i>Reardo noted</i>		
MONEY 12																
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TIME	05 SEP 2000															
DSC TH <i>Reardo noted</i>																

Date of mailing (day/month/year)	22.09.2000
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Applicant's or agent's file reference P005743WO CTH	REPLY DUE within 3 month(s) from the above date of mailing
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International application No. PCT/GB99/04295	International filing date (day/month/year) 17/12/1999	Priority date (day/month/year) 18/12/1998
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International Patent Classification (IPC) or both national classification and IPC A61K31/706

Applicant UNIVERSITY OF BATH et al.
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1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☒ Certain document cited
 - VII ☐ Certain defects in the international application
 - VIII ☒ Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
 For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
 For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **18/04/2001**.

Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer / Examiner Seegert, K <hr/> Formalities officer (incl. extension of time limits) Hundt, D Telephone No. +49 89 2399 8042
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I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-35 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 10 with respect to IA,

because:

- ☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,2,6-18
Inventive step (IS)	Claims	1-18
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

1. Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. Reference is made to the following documents:

- D1: WO 98 43992 A (UNIV BATH ;GALIONE ANTONY (GB); ISIS INNOVATION (GB); POTTER BARRY) 8 October 1998 (1998-10-08) cited in the application
- D2: GUSE A.H.: 'Ca²⁺ Signaling in T-Lymphocytes' CRITICAL REVIEWS IN IMMUNOLOGY, vol. 18, no. 5, 1998, pages 419-448, XP000872445
- D3: GUSE A.H. ET AL: 'Ca²⁺ Entry Induced by Cyclic ADP-ribose in Intact T-Lymphocytes' THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 13, 1997, pages 8546-8550, XP000872862

If not indicated otherwise, the relevant passages are those indicated in the International Search Report.

2. The subject-matter of the present application relates to the use of compounds capable of antagonising a sustained cADPR-mediated rise in intracellular Ca levels in a T-cell in the manufacture of a medicament for modulating T cell activity. The preferred compounds are cADPR analogues according to general formula (2). The preferred therapeutic application is the treatment of autoimmune diseases (claims 1 - 10). The application is further directed to screening methods (claims 11 - 13), to first medical uses (claim 14), to compounds (claim 15) and to processes (claims 16 - 18).
3. Document D1 discloses compounds of formula (2) and their cADP-ribose antagonising effects, e.g. in T-cells (see page 12, line 28 - page 13, line 1,

claims). According to figure 1 and page 22 of the description the activation of ADP-ribosyl cyclase activity is also tested. No therapeutic use is disclosed. Therefore the teaching of D1 is considered novelty destroying to the subject-matter of claims 11 - 13, 15 - 18.

4. Document D2 is a review article dealing with the Ca signalling effects in lymphocytes. In particular, D2 discloses that compounds of general formula (2) antagonise the cADPR induced calcium releasing effects in T-cells. D2 further teaches that the known immunosuppressant FK506 may act via this mechanism as well (see in particular page 425, right-hand column, penultimate paragraph). Finally in the conclusion on page 440 D2 suggests that the discovery of cADPR and its mechanism of activation of a channels in T-cells may have implication for the development of immune suppressive drugs.

The teaching of D2 is therefore considered novelty destroying to claims 1, 2, 6-10, 13-18 of the present application.

Summarizing the above, the subject-matter of claims 1, 2, 6-18 does not meet the novelty requirements of Article 33 (2) PCT.

5. As for claims 3 - 5, the novelty requirements of Article 33 (2) PCT are fulfilled, since the prior art does not disclose the specific compounds of formula (2) for therapeutic modulation of T cell activity. However, knowing from D2 that interference with cADPR would be therapeutically useful in immunosuppressant therapy and knowing further from e.g. D1 and D3 that these compounds have cADPR antagonistic effects, it would have been obvious to the skilled person to use these compounds for the indicated purpose. Therefore the requirements for inventive step as laid down in Article 33 (3) PCT are not met.
6. For the assessment of present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a

compound for the manufacture of a medicament for a new medical treatment.

Section VI

The following document may be considered relevant tin certain Contracting States:

EP-A-0 953 572 (priority: 28/04/98, filing: 28/04/99, publication: 03/11/99)

Section VIII

1. The functional definition of the compounds used in claims 1 and 2 is not sufficiently clear in order to enable the skilled person to perform the invention. It appears further that it would be an undue burden to the skilled person to find out which compounds are encompassed by the scope of the claims.
2. Similarly, the subject-matter of claim 15 lacks clarity since it is not defined by any technical features.
3. Claims 16 - 18 appear to relate to processes of manufacturing the compounds or compositions used in the present application, however without defining sufficient features for making them. Therefore these claims do not meet the requirements of Article 6 PCT.